Journal of the Formosan Medical Association (2013) 112, 749–755

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REVIEW ARTICLE

Chemical pleurodesis for spontaneous pneumothorax

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Received 9 September 2013; received in revised form 16 October 2013; accepted 17 October 2013

KEYWORDS
air leakage;
pleurodesis;
pneumothorax;
recurrence;
thoracoscopy

Pneumothorax is defined as the presence of air in the pleural cavity. Spontaneous pneumothorax, occurring without antecedent traumatic or iatrogenic cause, is sub-divided into primary and secondary. The severity of pneumothorax could be varied from asymptomatic to hemodynamically compromised. Optimal management of this benign disease has been a matter of debate. In addition to evacuating air from the pleural space by simple aspiration or chest tube drainage, the management of spontaneous pneumothorax also focused on ceasing air leakage and preventing recurrences by surgical intervention or chemical pleurodesis. Chemical pleurodesis is a procedure to achieve symphysis between the two layers of pleura by sclerosing agents. In the current practice guidelines, chemical pleurodesis is reserved for patients unable or unwilling to receive surgery. Recent researches have found that chemical pleurodesis is also safe and effective in preventing pneumothorax recurrence in patients with the first episode of spontaneous pneumothorax or after thoracoscopic surgery and treating persistent air leakage after thoracoscopic surgery. In this article we aimed at exploring the role of chemical pleurodesis for spontaneous pneumothorax, including ceasing air leakage and preventing recurrence. The indications, choice of sclerosants, safety, effects, and possible side effects or complications of chemical pleurodesis are also reviewed here.

Definition and classification of spontaneous pneumothorax

Pneumothorax, a common pleural disease worldwide, is defined as the presence of air in the pleural cavity, resulting in parenchymal collapse.[1] Pneumothorax can impair oxygenation and/or ventilation. If the pneumothorax is

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0929-6646/$ - see front matter
http://dx.doi.org/10.1016/j.jfma.2013.10.016

significant, it can cause a shift of the mediastinum and compromise hemodynamic stability. Clinically, pneumothorax is divided into spontaneous and traumatic. Spontaneous pneumothorax is sub-divided into primary and secondary, according to with or without precipitating underlying lung disease.[2–4]

Primary spontaneous pneumothorax (PSP), which is defined as a pneumothorax without obvious underlying lung disease, most commonly occurs in young, tall, lean males.[2,4] PSP occurs at a frequency of 7.4–18 cases per 100,000 population per year in men and in 1.2–6 cases per 100,000 population per year in women.[5,6] With regard to the etiology of PSP, anatomical abnormalities are commonly demonstrated at the apex of the lung. Emphysema-like changes, including subpleural blebs and bullae were found in 50–90% of PSP patients on high-resolution computed tomography (CT) scanning and in 76–100% of PSP patients during video-assisted thoracoscopic surgery (VATS) or thoracotomy.[7–12]

Secondary spontaneous pneumothorax (SSP) usually occurs in older people with underlying lung disease, such as emphysema, chronic obstructive lung disease, catamenial pneumothorax, cystic fibrosis, pulmonary infection, or lymphangioleiomyomatosis.[3,13–16]

Clinical presentation and diagnosis of spontaneous pneumothorax

Sudden onset of dyspnea and pleuritic chest pain were most complained.[17,18] The severity of the symptoms is primarily related to the volume of air in the pleural space. Symptoms are greater in SSP, even if the pneumothorax is relatively small in size.[4] Owing to the additional presence of the patient's underlying lung disease, SSP is considered a potentially life-threatening event, whereas PSP is virtually always a nuisance rather than a life-threatening condition.[19]

Diagnosis of pneumothorax is confirmed by imaging studies, primarily a plain chest film obtained during forced inspiration with the patient in a standing position.[20,21] The presence of a pneumothorax is established by demonstrating a white visceral pleural line on the chest radiograph. Inspiratory and expiratory films have equal sensitivity in detecting pneumothoraces; thus, a standard inspiratory chest radiograph is sufficient in most cases.

The percentage of collapsed lung can be estimated using a plain chest film by the measurement of the average diameter of the collapsed lung and the involved hemithorax (Light's formula).[22]

Although chest CT scans can reveal the underlying pathophysiologic lesions that cause spontaneous pneumothorax and can be regarded as the "gold standard" in the detection of small pneumothoraces and in size estimation,[23,24] the American Collage of Chest Physicians (ACCP) does not recommend the routine use of this imaging technique for patients with first-time primary or secondary pneumothoraces.[21] CT may, however, be useful for evaluating patients with recurrent secondary pneumothorax, to determine the best treatment for persistent air leakage, or to plan a surgical intervention.[25] The British Thoracic Society (BTS) recommends using CT when required to differentiate between pneumothorax and bullous lung disease, when aberrant tube placement is suspected and when the plain chest radiograph is difficult to read owing to the presence of subcutaneous emphysema.[4]

Treatment options for spontaneous pneumothorax

The management of pneumothorax focused on evacuating air from the pleural space, ceasing air leakage, and preventing recurrences.[4,19,21] Available therapeutic options include observation, simple aspiration, intercostal drainage with a pigtail catheter or chest tube, intercostal drainage with chemical pleurodesis, medical thoracoscopy with chemical pleurodesis, or surgical intervention (VATS or thoracotomy) with/without chemical pleurodesis. The selection of an approach depends on the size of the pneumothorax, the severity of symptoms, whether there is a persistent air leakage, and whether the pneumothorax is primary or secondary.[4,19,21] Generally, surgical intervention is reserved for patients with recurrent or complicated spontaneous pneumothorax, and chemical pleurodesis can be used as an adjunct after drainage or surgery.

Chemical pleurodesis

Pleurodesis is a procedure to achieve symphysis between the two layers of pleura to prevent recurrent pleural effusion or recurrent pneumothorax.[4,26,27] Either instilling a chemical irritant (chemical pleurodesis) or performing mechanical abrasion (mechanical pleurodesis) that induced inflammation and fibrosis caused the symphysis between the two layers of pleura.[8] Clinically, chemical pleurodesis was widely applied for stopping air-leak or for preventing pneumothorax recurrence. Chemical pleurodesis can be applied through the intercostal drainage tube, medical thoracoscopy, or during the operation. In clinical practice, a variety of sclerosants have been used, including tetracycline and derivatives (doxycycline or minocycline), talc, bleomycin, autologous blood patch, iodopovidone, picibanil, silver nitrate, and quinacrine.[27–31] In a survey from five English-speaking countries (United States, United Kingdom, Canada, Australia, and New Zealand), the most commonly used agent was talc followed by tetracycline derivatives and bleomycin.[32]

Chemical pleurodesis for persistent air leakage after chest drainage

Persistent air leakage is defined as air leakage more than 5–7 days after intercostal drainage, which are more common with secondary pneumothorax than with primary pneumothorax.[33–35] For patients with persistent air leakage, physicians must consider surgical intervention to prevent prolonged hospitalization and the possibility of a recurrent pneumothorax.[4,19,21] VATS has been advocated in the management of patients with PSP and the selection of patients with SSP who suffer from persistent air leakage.[33,36–39] For patient has objective evidence of

inoperable condition, chemical pleurodesis is a reasonable option.

In 1994, Alfageme et al[40] reported that the intrapleural instillation of tetracycline has 60% of success rate among spontaneous pneumothorax patients with persistent air leakage. Cagirici et al[41] in 1998 conducted a prospective randomized study to examine the efficacy of autologous blood patch pleurodesis when compared with tube thoracostomy alone. Air leakage resolution occurred in 84% of patients within 72 hours and was significantly reduced when compared with tube thoracostomy alone.

Chemical pleurodesis for preventing pneumothorax recurrence

One of the most important issues of managing spontaneous pneumothorax is to prevent pneumothorax recurrence. The 1-year recurrence rate in PSP patients with the first episode using chest tube drainage is around 30% (16—52%) and progressively increases after the second or third episode.[19,42] Although chemical pleurodesis effectively reduces the recurrence of spontaneous pneumothorax in surgical and nonsurgical patients,[22,43—45] published guidelines do not recommend it as the initial treatment for primary spontaneous pneumothorax.[4,19—21]

In a recent published clinical trial, Chen et al[46] randomized patients with the first episode of PSP to simple aspiration/drainage only (control, $n = 108$) or simple aspiration/drainage and minocycline pleurodesis ($n = 106$). After a follow-up for at least 12 months, pneumothorax recurrence was lower in the minocycline group (29.2%) compared with controls (49.1%), which led to fewer subsequent surgical interventions.[46] Autologous blood patch pleurodesis maybe also effective to prevent pneumothorax recurrence. The pneumothorax recurrence rate following autologous blood patch pleurodesis ranged from 0% to 29%, in comparison with tube thoracostomy alone 35—41%.[47—49]

Although surgical treatment is the most effective way in treating spontaneous pneumothorax, 5—15% of patients developed pneumothorax recurrence after thoracoscopic surgery, which is significantly higher compared with thoracotomy (0—1%).[4,44,50,51] The possible explanations have included inadequate exposure of chest cavity and decreased severity of pleural inflammation caused by thoracoscopy than by thoracotomy.[36,44] Loubani et al[52] reported significant reduced rates of pneumothorax recurrence in patients who underwent thoracoscopic staple bullectomy alone (20%) against those who received bullectomy and tetracycline pleurodesis (4%). Similar result was also reported by Chen et al[43,44] that additional minocycline pleurodesis after thoracoscopic surgery had lower pneumothorax recurrence compared with thoracoscopic surgery alone.

Chemical pleurodesis for postoperative air leakage after surgery for pneumothorax

Prolonged air leakage is the most common complication, range from 7% to 14%, following thoracoscopic treatment for PSP, and the optimal management is rarely mentioned.[35,53—55] Recently, How et al[55] reported that chemical pleurodesis using OK-432 or minocycline were effective to cease air leakage for patients of PSP with prolonged air leakage after thoracoscopic surgery. Furthermore, patients undergoing OK-432 pleurodesis seems to be more effective by having shorter durations of post pleurodesis chest drainage and postoperative hospital stay than those undergoing minocycline pleurodesis.[55]

Sclerosing agents for chemical pleurodesis

Talc

At the present time, talc is one of the agents most commonly used for chemical pleurodesis in patients with either a spontaneous pneumothorax or a recurrent pleural effusion, even though the occasional reports of severe side effects.[32,56] There are at least 32 cases of adult respiratory failure syndrome (ARDS) following intrapleural talc administration in the literature, 17 following the use of talc slurry, and the remaining 15 following talc insufflation.[56—58]

The development of ARDS after talc pleurodesis was later found to be related to the size of the particles as well as the employed doses. In a multicentre prospective study conducted by Bridevaux et al,[59] including 418 patients diagnosed with spontaneous pneumothorax, neither ARDS nor pneumonitis cases were reported using low doses of talc (2 g) and medium-sized particles (31.5 μm).

Empyema is also reported after talc pleurodesis, which may be related to techniques used for the sterilization of talc.[60,61] The other concern regarding the potential effect of long-term pulmonary function by talc pleurodesis on young pneumothorax patients has been addressed. Although Lange et al[28] showed only a mild restrictive respiratory impairment at a follow-up of 22—35 years, Dubois et al[53] showed that thoracoscopic apical bullectomy and talc poudrage would cause changes in pulmonary function at 1 year.

Another important concern in patients undergoing talc pleurodesis is the possibility of false positives in the interpretation of fluorine 18 (18 F) flurorodeoxyglucose (FDG) due to a high capitation of FDG in the acute and chronic phases of pleural inflammation, leading to pleural symphysis or the appearance of pleural pseudotumoral granulomatous (talcoma) or pseudosarcomatous reactions, similar to primary malignant tumoral or metastatic lesions with increased metabolic activity as reported by the positron emission tomography-computed tomography (PET-CT).[62]

Tetracycline and minocycline

Tetracycline, which was the most commonly used irritant,[22] is no longer available. Minocycline, a derivative of tetracycline, is as effective as tetracycline in inducing pleural fibrosis in rabbits.[63] No major complication or mortality was associated with chemical pleurodesis using minocycline. The main disadvantage of minocycline is immediate chest pain after instillation, which is relieved spontaneously within several hours and does not impair pulmonary function or increase the risk of residual chest pain 6 months after the operation.[43,44]

Bleomycin

Bleomycin was widely used for the treatment of malignant pleural effusions because of its antineoplastic actions and because it appeared comparable in effectiveness to tetracycline in the treatment of malignant pleural effusions.[64,65] In an animal study, Vargas et al[64] revealed that the intrapleural injection of bleomycin was ineffective in creating pleural fibrosis, either grossly or microscopically. As bleomycin is expensive and relatively ineffective compared with other sclerosing agents,[31] it is not recommended be used as a pleural sclerosant in patients with non-neoplastic pleural disease, such as pneumothorax, congestive heart failure, or liver cirrhosis.[64]

Autologous blood patch

In contrast to other chemical irritants for pleurodesis such as talc or tetracycline, autologous blood patch does not cause systemic inflammatory reactions or severe pain. The procedure of pleurodesis with autologous blood was as following: 50 mL of autologous blood without anticoagulant was obtained from each patient. As soon as the blood was drawn, it was immediately injected into the pleural space through a chest tube.[66] Although transient fever may develop following autologous blood patch pleurodesis,[48,67] most authors emphasized that no major complication was observed.[49] Other possible complications of autologous blood patch pleurodesis have included empyema and pleural effusions.[41] However, a reported case of tension pneumothorax highlights the potential risk for an obstructing clot in the chest tube.[68]

OK-432 (Picibanil)

OK-432 (*Picibanil*), a lyophilized mixture of a low virulence strain (Su) of *Streptococcus pyogenes* incubated with benzylpenicillin, has been used in sclerotherapy for neck lymphangioma, malignant pleural effusion, and intractable pneumothorax with satisfactory results.[69–71] No major complication of pleurodesis using picibanil was reported. The main side effects of the pleurodesis with picibanil were fever and chest pain, which were well controlled by nonsteroidal anti-inflammatory drugs.[55,69]

Iodopovidone

Iodopovidone is a topical antiseptic and has been shown to be safe and effective in several studies.[30,31,72] A solution containing a mixture of 20-mL 10% iodopovidone and 80-mL normal saline was used to create pleurodesis. Iodopovidone pleurodesis is generally safe. The most common side effect

Table 1 Indications, effects, and complications of chemical pleurodesis for spontaneous pneumothorax.

Sclerosing agent	Indications	Effect	Side effects and complications
Talc[28,30,45,53,58–61,74,75]	Initial treatment for PSP and SSP	Decreased pneumothorax recurrence to 0–9%	Chest pain (7–15.6%), fever (1.6–63.2%), dyspnea (57.9%), pleural effusion (1.2%), pneumonia (0.5–0.9%), hemothorax (0.9%), and ARDS (0–9%)
Autologous blood patch[29,34,41,47–49,66–68]	Initial treatment for PSP and SSP	Ceasing air leakage in 75–93% Decreased pneumothorax recurrence to 0–29% after VATS	Empyema (5–9.4%), pleural effusion (5–15.6%), and fever (10–12.5%)
Tetracycline[22,27,40,76]	Initial treatment for PSP and SSP	Decreased pneumothorax recurrence to 9–25%	Chest pain (33–90%), fever (9–81%), dyspnea (36%), and elevated liver enzyme (45%)
Minocycline[55]	Prolonged air leakage for PSP after VATS	Ceasing air leakage in 63%	Chest pain, fever (1%), and loculated effusion (1.7%)
Minocycline[11,46]	Initial treatment for PSP	Decreased pneumothorax recurrence to 13–29%	Chest pain (67%)
Minocycline[43,44,77]	Adjuvant treatment for PSP after VATS	Decreased pneumothorax recurrence to 2–4%	Chest pain (44.6–83.5%), fever (4.1%), and hemothorax (0.6%)
Povidone-iodine[30,72,73]	Initial treatment for PSP and SSP	Decreased pneumothorax recurrence to 0–6%	Chest pain (13%), fever (6.1–33%), empyema, and wound infection (2.4%)
Picibanil[55,69]	Adjuvant treatment for PSP after VATS and initial treatment for SSP	Ceasing air leakage in 95% and decreased pneumothorax recurrence to 5% after VATS	Chest pain and fever (21%)

ARDS = acute respiratory distress syndrome; PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax; VATS = video-assisted thoracoscopic surgery.

is chest pain. Fever and empyema were also mentioned in some studies with low incidence.[72,73]

Conclusions and future perspectives

Although there are many options in the management of spontaneous pneumothorax, chemical pleurodesis should play a more important role in this benign disease. The most updated clinical trial showed that minocycline pleurodesis effectively reduces pneumothorax recurrence and subsequent thoracoscopic surgery in the first episode of PSP. For pneumothorax patients suffered from persistent air leakage, pleurodesis using autologous blood patch, talc, and picibanil are safe and effective. Additional chemical pleurodesis following VATS bullectomy was also effective to reduce the pneumothorax recurrence rate in PSP patients. More and more clinical evidence showed that chemical pleurodesis through a drainage tube/catheter is easy, safe, and cost-effective for the treatment of spontaneous pneumothorax. The optimal timing and choice of chemical pleurodesis for spontaneous pneumothorax, however, depends on the patient's condition, physician's experience, and availability of sclerosants. The indications, effects, and complications of common sclerosing agents are summarized in Table 1.[11,22,27–30,34,40,41,43–49,53,55,58–61,66–69,72–77] Future studies should focus on the comparison of safety and efficacy of different sclerosing agents in specific clinical settings of spontaneous pneumothorax.

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